

The Problem

- It is likely that widespread genetic testing will soon be available. There are only a small number of clinical geneticists and counselors in the United States. Only a small percentage of the population has even the most basic understanding of genetics. This applies to mental health professionals as well.

The Basics

- Deoxyribonucleic acid (DNA) is found in the nucleus of every cell. Each DNA molecule is made of two strands with 4 bases (adenine, thymine, guanine, and cytosine. A-T and G-C are base pairs.) The two strands twist like a ribbon into a shape called a double helix.

Chromosomes and Genes

- A piece of DNA 50-250 million base pairs long is called a chromosome. Humans inherit 23 chromosomes from each parent.
- On each chromosome, there are thousands of genes.
- Altogether, we have about 25,000 genes, which provide the instructions to making a human being. The set of our genes is called the human genome. In April 2003, a high quality mapping of the human genome was completed.

The Human Genome

- Genes comprise only 2% of the material in our chromosomes. The function of 98% of DNA is not well understood
- Furthermore, the function of more than 50% of discovered genes is unknown.
- We do know that 99.9% of the human genome is identical in all human beings. The 0.1% variation in people is inherited in units known as haploid genotypes, or haplotypes. A mapping of these areas will provide an understanding of the causes of many illnesses.

Genetic Illness

- Some defective genes directly cause illness (sickle cell anemia, Huntington's disease, cystic fibrosis), and there is no impact from the environment. In this case, the association of disease to gene may be said to have an "odds ratio" of 100.
- There are no psychiatric disorders caused by any genes in this Mendelian fashion.

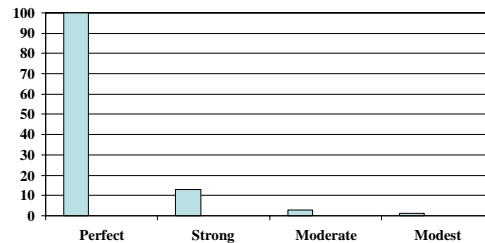
Genetic Illness Odds Ratios

- Very strong association
 - Smoking and small cell lung carcinoma (20)
 - Asbestos and mesothelioma (15)
 - Stressful life events and depression (12)
- Moderate association
 - ApoE4 allele and Alzheimer's disease (3)
 - ALDH2*2 and alcoholism reduction (3)

Genetic Illness

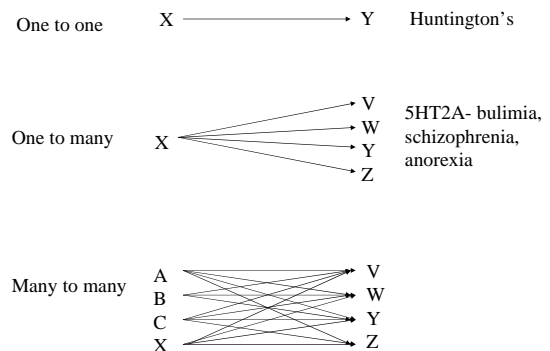
- Modest association
 - DRD5 dinucleotide repeat and ADHD (1.57)
 - DRD2 Ser311Cys and schizophrenia (1.43)
 - 5-HT2AR 1438G/A and anorexia nervosa (1.42)
 - 5-HT2AR 1438G/A and bulimia (1.33)
 - 5-HTT 44 base pair insertion and bipolar (1.14)

Odds Ratios for Genetic Association



X is a Gene for Y

- For psychiatric disorders, individual genes have quite a modest association with the illness.
- In addition, there is no evidence of causal specificity between gene and psychiatric illness, that is, one gene causes a certain behavioral outcome.



Environmental Contingencies

- Even in illnesses that are 100% heritable, expression of the gene may be environmental. (PKU)
- In psychiatry, there is stronger evidence for the specificity of environmental effects than genetic effects, e.g. what distinguishes the behavioral symptoms of anxiety and depression, with moderate specificity, are environmental factors.
- Unfortunately, environmental contingencies for genetic effects on psychiatric disorders have not yet been regularly investigated.

Environmental Contingencies

- Genes can actually be turned on and off by influences in the environment. Microarray analysis is enabling researches to determine which genes are functioning and which are not in contrasting populations:
 - Long term alcoholics
 - People taking antidepressants
 - Children with affectionate vs. abusive parents

The Environment

- At least three well-documented examples of the environment modifying specific genetic expression have been documented.

Monoamine Oxidase

- Monoamine oxidase breaks down dopamine, norepinephrine, and epinephrine in the synapses between nerve cells.
- There are two types of MAO coded for on the X chromosome: A and B.
- Animals with the gene for MAO-A “knocked out” are more violent than those with an MAO-A gene that functions.
- Children with the MAO-A variant in abusive homes become violent.

Serotonin Transporter

- The gene that codes for the serotonin transporter, which removes serotonin from the synaptic cleft between nerve cells, has two alleles: long (l) and short (s).
- Mice with genetically disrupted serotonin transporter genes show more fearful behavior when exposed to stress.
- People with the ss variant become depressed in a stressful environment.

Catechol *O*-methyltransferase

- Catechol *O*-methyltransferase breaks down dopamine and norepinephrine between nerve cells.
- There are two alleles for COMT - valine (val) and methionine (met).
- People with the val alleles were found to be at higher risk for substance abuse disorders, but only when exposed to those substances.

Some Genes Modify Our Environment

- Not only can the environment effect gene expression, but gene expression also effects the environment:
 - Temperament
 - Appearance
 - Gender

Gender

Gene SRY on tip of Y chromosome: 612 bases long, becomes a protein: testis determining factor. It is switched on in the brain and in the testis on day 11 after conception for a few hours. It switches on one other gene: SOX9

SOX9

- SOX9 switches on and off many different genes: Lhx9, Wt1, Sfl, Dax1, Gata4, Dmrt1, Amh, Wnt4, Dhh.
- These genes effect the development of hormones, proteins, and change the expression of other genes. They are reactive in specific ways to diet, social stimulation, and stress creating an organism with a greater tendency to take risks, act violently, and die young of heart disease.

X is a Gene for Y?

- Not in behavioral genetics! There is no Mendelian genetic relationship for psychiatric disorders, and there is unlikely to be one discovered. Instead, what is more likely is that we will find out that genes cause certain biological features that then may create vulnerabilities for a number of different disorders, depending on environmental influences.

Terminology

- We know that mental illnesses are, nonetheless, inherited. What do we know?
- h^2 - heritability coefficient. How much difference between people is directly attributable to genetic difference?
- c^2 - shared environmental effects. How much of the difference between people is directly attributable to their family environment?
- e^2 - nonshared environment

Techniques

- There are two kinds of methods used to determine whether a condition is inherited:
 - Molecular genetics - linkage, association studies
 - Genetic effect measurements - parent/child, twin studies, adoption studies
- Both require very sophisticated statistical analysis.

Preliminary Results

- So far, the data gathered regarding the heritability of mental disorders indicates that our current system of definition of a disorder by symptom cluster does not reflect the underlying biological process. Inheritance data reflects functional imaging abnormalities better than diagnostic categories.
- Data support a dimensional model, with emphasis placed on some symptoms rather than named disease, in a different hierarchical structure, and more emphasis on environmental exposure.

Present Data

- h^2 of severe depression: 70%
- h^2 of moderate, common depression: 30-40%
- Most heritable
 - Sleep problems, libido, appetite, loss of energy
- Least heritable
 - Loneliness, tearfulness, somatic symptoms

Present Data

- h^2 of bipolar I: 60-70%
- Bipolar I looks like an extreme form of unipolar illness - similar genetic factors. The difference may be environmental.
- The role of genetic effects is to sensitize people to the influence of depressogenic events. The primary risk factors for the onset of major depression are:
 - Stressful event in the last year, genetics, previous history of depression, neurotic personality trait.

Present Data

- Genetic data supports the five factor model of personality (neuroticism, extraversion, openness, agreeableness, conscientiousness) with similar inheritance patterns for normal and abnormal personality. This is at odds with the current view of “types” described by DSM Axis II.
- Heritability analyses have consistently identified nonshared environmental influences as the most important variable in individual personality.
- Genetic effects: 40-45%

Present Data

- Genetic analysis has described four genetic and environmental factors of personality dysfunction:
 - Emotional dysregulation (neuroticism)
 - Inhibition (extraversion)
 - Antisocial (agreeableness)
 - Conscientiousness (conscientiousness)
- Openness does not seem to have a pathological extreme.

Present Data

- The anxiety disorders are all moderately heritable ($h^2 \sim 30\%$) with the majority of effect being nonshared environmental (e^2).
- GAD is most closely related to depression. What distinguishes GAD from depression is specific environmental exposure (danger vs. loss).
- Avoidant personality disorder is probably an extreme form of social phobia.

Present Data

- Obsessions and compulsions only partially come from the same genetic causes.
- Although PTSD has a heritable component, the most important risk factors are environmental (quality and kind of exposure.) Exposure to specific events may be mediated by genes:
 - h^2 marital problems - 14%
 - h^2 victim of robbery/assault - 33%
 - h^2 financial problems - 18%
 - h^2 illness/injury - 21%
 - h^2 problems at work - 18%

Present Data

- Anxiety disorders are not acquired simply by being exposed to different kinds of threatening events. Genetic factors influence the rate and sensitivity by which fear associations are made or extinguished.

Present Data

- Alcoholism:
 - h^2 : 45-50%, c^2 : 10-15%, e^2 : 30-40%
- Nicotine dependence:
 - h^2 : 42.2%, c^2 : 8-10%, e^2 : 45-50%
- Illicit drug dependence:
 - c^2 is high for initiation (religious beliefs, parental monitoring, parental and sibling use...)
 - Other genetic factors influence continuing use.

Present Data

- Genetic covariance of behavioral undercontrol, childhood conduct disorder and alcoholism: 85% in males, 93% in females!
- Religious beliefs, marriage and urban (h^2 factors more important) and rural (c^2 more important) setting modifies genetic risk.

Present Data

- Schizophrenia shows the highest degree of inheritability of any psychiatric disorder: h^2 : 82-85%, c^2 : ~0, e^2 : 15% (season of birth, viral infection, urban density...)
- Single gene models do not explain the pattern of inheritance for schizophrenia.
- There is evidence that the environment can exert a protective effect on the development of schizophrenia.

Pharmacogenomics

- Certain variations in genes affect the metabolism of medications. If the metabolism is slowed down, too much drug can accumulate and may be fatal. If metabolism is speeded up, the drug may not be effective at normal doses.
- The cytochrome p450 family of genes, expressed primarily in the liver, affect psychotropic and other medications. There are three main ones:
 - CYP3A4 - lots of drug effects, few polymorphism
 - CYP2D6 - lots of drug effects, lots of polymorphism
 - CYP2C19 - few effects, lots of polymorphism

CYP 2D6

- Antidepressants:
 - desipramine, fluoxetine, nortriptyline, paroxetine, venlafaxine
- Antipsychotics:
 - fluphenazine, perphenazine, risperidone
- Stimulants
 - atomoxetine
- Other
 - codeine, dextromethorphan, oxycodone
 - beta blockers

2C19

- Antidepressants
 - amitriptyline, clomipramine, imipramine, citalopram, escitalopram, sertraline
- Benzodiazepines
 - diazepam
- Other
 - phenytoin
 - propranolol

Biodiagnostics

- The s allele of the serotonin transporter gene has been associated with depression and suicidality.
- Subjects with the s allele underwent neuroimaging show reduced gray matter volume in certain areas of the limbic system of the brain. fMRI revealed hyperactivity of the amygdala when presented with a fearful stimulus.
- This provides new diagnostic methods for finding at risk subjects, and increased understanding of the pathophysiology of disease.

Pharmacogenomics, again

- Knowing the molecular basis of disease will allow the construction of new generations of psychotropic medications that will not be simply treating symptoms, but will treat the illness.

Gene Therapy

- Viruses are used to carry a corrective gene into cells. The cells then replicate with the normal gene.
- Currently, gene therapy has not proven to be useful. Three children have died as a result of attempted gene therapy (immune response, leukemia).

Ethical Issues in Genetics

- Privacy
- Insurance/workplace discrimination
- Testing for psychiatric disorders
- Patenting
- Research

Thoughts About Treatment

- We can increase our tolerance and client's self-acceptance by understanding that we don't choose our temperament, or our illnesses. At the same time, by understanding how environment modifies the expression of our genes, our clients can be empowered to make changes that can affect their lives.